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Synthesis of the Proposed Isomers of the Deep-Sea Mussel Metabolites Bathymodiolamides A and B

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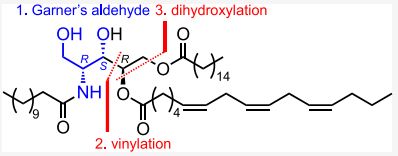
ABSTRACT: The first total synthesis of bathymodiolamides A and B, ceramide-like metabolites of the deep-sea hydrothermal vent mussel *Bathymodiolus thermophilus*, was accomplished in eight linear steps starting from Garner's aldehyde and three carboxylic acids. A sequence of vinylation of Garner's aldehyde, N-acylation with lauric acid, dihydroxylation of the terminal alkene, and stepwise Steglich−Hassner esterifications of the resulting vicinal diol with the respective saturated and unsaturated carboxylic acids, which had to be prepared separately, afforded the target products in 38 and 39% yield. We found distinct discrepancies between their NMR data and antiproliferative activities and those reported for the natural isolates.



INTRODUCTION

The bathymodiolamides A (**1**) and B (**2**) are ceramide-related lipid metabolites that were isolated from the deep-sea hydrothermal vent mussel *Bathymodiolus thermophilus*.[1] Their absolute configurations were deduced based on NMR and mass spectra, chemical degradation, and on a comparison of specific optical rotations of related known compounds. These data suggested the absolute configurations of the stereotriad of **1** and **2** to be identical to those of the known congener L-arabino phytosphingosine (**3**),[2] that is, 2*R*,3*S*,4*R* (Figure 1). Because of their distinct apoptosis induction and cytotoxic effect in cancer cells, they and further structurally related metabolites from the same source organism were recently patented for potential use in cancer chemotherapy.[3] We now report a short flexible synthetic route to the proposed (2*R*,3*S*,4*R*)-isomers of bathymodiolamides A and B, and a comparison of their physical data and anticancer activities with those reported for the natural isolates.

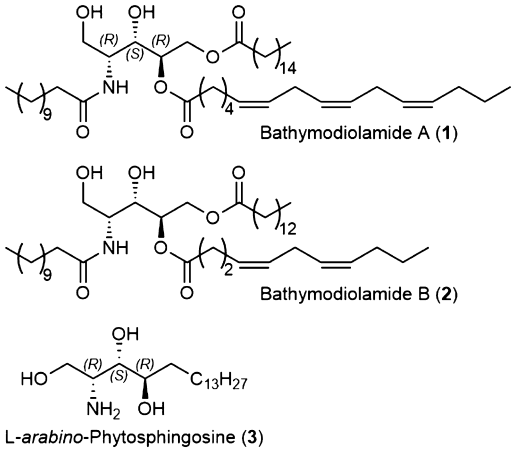
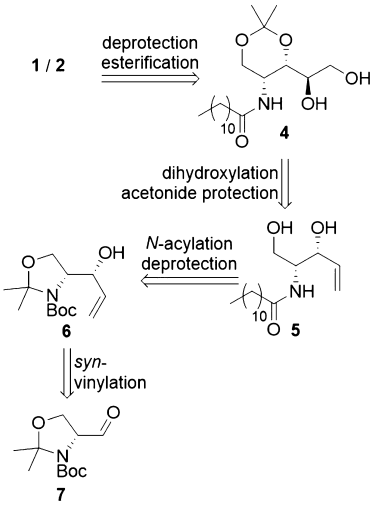


Figure 1. Structures of bathymodiolamides A (**1**) and B (**2**) and L-arabino phytosphingosine (**3**).

RESULTS AND DISCUSSION

Our retrosynthetic approach is outlined in Scheme 1. Both target compounds **1** and **2** were finished by consecutive attachment of the corresponding saturated and unsaturated

Scheme 1. Retrosynthesis of Bathymodiolamides A (1) and B (2)



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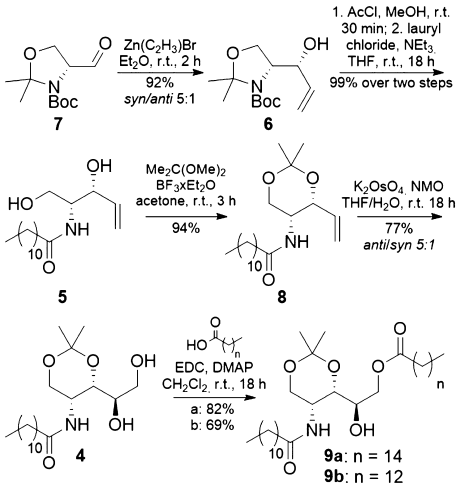
carboxylic acids to diol **4** followed by acetonide deprotection. Acetonide protection of amide **5** and asymmetric dihydroxylation of the alkene under substrate control should predominantly furnish diol **4**, thus installing stereogenic center 4*R*. Amide **5** was accessible by deprotection and N-acylation of allylic alcohol **6** which contributes stereogenic center 3*S*, established by *syn*-selective vinylation of *R*-Garner's aldehyde (**7**). The latter is readily available from D-serine[4] and served as a source of carbon atoms C1−C3 and of stereogenic center 2*R*.

Vinylation of **7** with vinyl zinc bromide according to modified literature procedures[5] and purification by column chromatography afforded the *syn*-configured allylic alcohol **6** in 92% yield (Scheme 2). It was treated with a mixture of acetyl

Scheme 2. Synthesis of Diol 4 and Its Mono Esters 9a and 9b

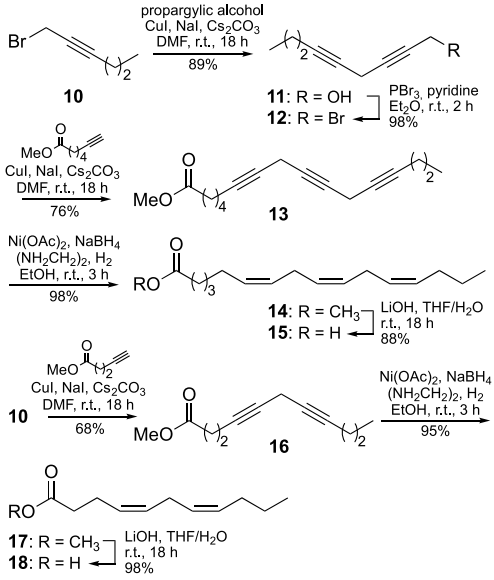


chloride and methanol to cleave the boc and the aminal groups resulting in an amine which was acylated right away with commercially available lauryl chloride to give amide **5** in 99% yield. Acetonide protection of its hydroxy groups left alkene **8** which was dihydroxylated under substrate control with potassium osmate/NMO furnishing predominantly diol **4** with a syn/anti ratio of 1:5. Gratifyingly, **4** was easy to purify *via* column chromatography and the absolute configuration of the secondary alcohol was ascertained to be *R* by analysis of the ^{1}H NMR spectra of the corresponding Mosher esters (*cf.* Supporting Information for details).[6] The primary hydroxy group of **4** was then esterified with palmitic acid or myristic acid under Steglich−Hassner conditions affording the hydroxyesters **9a** and **9b** in 82 and 69% yield.

The required skipped trienoic and dienoic acids **15** and **18** were both prepared starting from readily available 1-bromohex-2-yne (**10**)[7] (Scheme 3). The copper-mediated coupling of **10** with propargylic alcohol afforded alcohol **11**, which in turn was converted into propargylic bromide **12**. Coupling of **12** with 6-heptynoic acid methyl ester[8] gave triyne **13**. *Z*-selective reduction of **13** according to Brown's P-2 Ni protocol[9] and saponification of resulting ester **14** led to hexadeca-6*Z*,9*Z*,12*Z*-trienoic acid (**15**) in 57% overall yield. Undeca-4*Z*,7*Z*-dienoic acid (**18**) was prepared analogously in 63% overall yield by coupling **10** with 4-pentynoic acid methyl ester[10] followed by *Z*-selective reduction of diyne **16** and saponification of ester **17**.

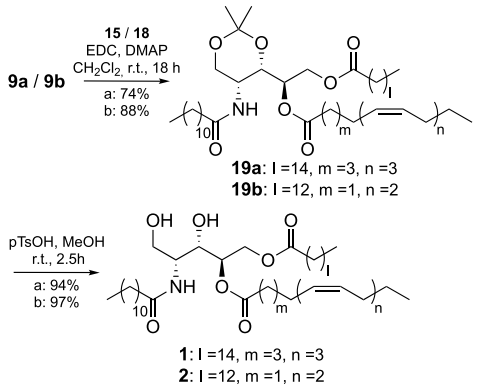
To complete the synthesis, hydroxy esters **9a** and **9b** were esterified with the respective oligoenoic acid **15** or **18**, again

Scheme 3. Synthesis of Skipped Polyunsaturated Fatty Acids 15 and 18



under Steglich−Hassner conditions, to afford the diester amides **19a** and **19b** which were eventually deprotected with pTsOH in methanol to give the target compounds **1** and **2** in 38 and 39% overall yield (Scheme 4). Their specific optical

Scheme 4. Final Steps Affording (2*R*,3*S*,4*R*)-Bathymodiolamides A (1) and B (2)



rotations of $[\alpha]_D^{23}$ +14.8 (*c* 0.08 in MeOH) for **1** and $[\alpha]_D^{23}$ +6.7 (*c* 0.08 in MeOH) for **2** deviated somewhat from $[\alpha]_D^{23}$ +10.8 (*c* 0.08 in MeOH)[1] as reported for both natural isolates. Even more conspicuous are the differences in the ^{1}H and ^{13}C NMR spectra of our synthetic products when compared with those reported by Andrianasolo *et al.*,[1] for the natural isolates, in particular, the marked differences in the chemical shifts of the atoms of the aminotetraol moiety and in some coupling constants in the ^{1}H NMR spectra (*cf.* Table 1, Supporting Information). This casts some doubt on the stereochemical assignment of the aminotetraol moiety of the isolates.

The isolating group also reported the cytotoxicities of **1** and **2** as measured via a modified MTT assay. They found an IC_{50} = 0.4 μM for **1** and 0.5 μM for **2** against HeLa cervical cancer cells and an IC_{50} = 0.1 μM for **1** and 0.2 μM for **2** against MCF7 breast carcinoma cells.[1] We tested our synthetic products **1** and **2** for antiproliferative effects in MTT assays against cells of HeLa, MCF7, as well as HCT-116 and its p53

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J. Org. Chem. 2021, 86, 1868−1873

mutant HCT-116$^{p53-/-}$ colon carcinoma, 518A2 human melanoma, and U87 human glioblastoma. However, both were virtually inactive with IC_{50} > 50 μM in all tested cancer cell lines (*cf.* Table 2, Supporting Information). This inactivity suggests a possibly incorrect structural assignment for both natural compounds.

CONCLUSIONS

In summary, we developed efficient eight-step syntheses for the (2*R*,3*S*,4*R*)-isomers purported for the natural bathymodiolamides A and B. However, discrepancies in the NMR data and *in vitro* anticancer activities of our synthetic products and those reported for the natural isolates suggest a re-evaluation of the latter. As our synthetic route is straightforward and sufficiently flexible to allow the synthesis of other stereoisomers of **1** and **2**, it could be used to clarify the configurations of the natural bathymodiolamides A and B and to establish reliable structure−activity relationships.

EXPERIMENTAL SECTION

General Remarks. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker DRX 500 spectrometer. Chemical shifts are given in parts per million using the residual solvent peak as an internal standard 7.26 ppm (proton) and 77.00 ppm (carbon) for $CDCl_3$ and 3.31 ppm (proton) and 49.15 ppm (carbon) for MeOD. Coupling constants (*J*) are quoted in Hz. Multiplicity abbreviation used: s singlet, d doublet, t triplet, q quartet, quin quintet, sxt sextet, and m multiplet. High-resolution mass spectra were obtained with a UPLC/Orbitrap MS system in electrospray ionization (ESI) mode. IR spectra were recorded with a Perkin-Elmer Spectrum 100 FT-IR spectrophotometer with an ATR sampling unit. Optical rotations were measured at 589 nm (Na D line) on a PerkinElmer 241 polarimeter. Melting points were obtained by a Büchi melting point M-565 and are uncorrected. All reagents were purchased from commercial sources and were used without further purification. All anhydrous solvents were used as supplied, except tetrahydrofuran and dichloromethane which were freshly distilled according to standard procedures. Reactions were routinely carried out under an argon atmosphere unless stated otherwise. All glassware was flame-dried before use. Analytical thin layer chromatography was carried out using Merck Kieselgel 60GF254 pre-coated aluminum-backed plates. The compounds were visualized with UV light (25 and/or 360 nm) and/or potassium permanganate. Flash chromatography was performed at medium pressure using Macherey-Nagel silica gel 60, pore size 40−63 μm with the eluent specified. (*R*)-Garner's aldehyde (**7**),[4] 1-bromohex-2-yne (**10**),[7] 6-heptynoic acid methyl ester,[8] and 4-pentynoic acid methyl ester[10] were prepared according to literature procedures.

tert-Butyl (*R*)-4-((*R*)-1-hydroxyallyl)-2,2-dimethyloxazolidine-3-carboxylate (**6**) was prepared according to a modified literature procedure.[5a] Tetravinyltin (2.0 mL, 10.9 mmol) in dry Et_2O (50 mL) was treated with MeLi (27.3 mL, 1.6M in Et_2O, 43.6 mmol) at 0 °C. The mixture was stirred for 15 min at 0 °C before $ZnBr_2$ (9.8 g, 43.6 mmol) was added. After stirring for 1 h at ambient temperature, the mixture was added to a solution of (*R*)-Garner's aldehyde (**7**) (2.5 g, 10.9 mmol) and $ZnBr_2$ (2.5 g, 10.9 mmol) in dry Et_2O (50 mL) at −35 °C. The mixture was allowed to warm to ambient temperature and stirred for 3 h. Saturated aqueous NH_4Cl (100 mL) was added, and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 100 mL). The combined organic phases were washed with brine (200 mL), dried over $MgSO_4$, and evaporated to dryness. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate 5:1) to give **6** (2.58 g, 10.0 mmol, 92%) as a white solid; analytical data agreed with those reported.[5a]

*N-((2R,3R)-1,3-Dihydroxypent-4-en-2-yl)dodecanamide (**5**).* A solution of **6** (1.5 g, 5.8 mmol) in MeOH (30 mL) was treated with 2 mL AcCl at 0 °C. The mixture was stirred for 30 min at room temperature and volatiles were evaporated. The residue was taken up in THF (30 mL), and NEt_3 (2.4 mL, 17.49 mmol) and lauroyl chloride (1.5 mL, 6.41 mmol) were added. The mixture was stirred for 18 h at room temperature, then diluted with EtOAc (50 mL), and the organic phase was washed with 1 M HCl (75 mL), aqueous $NaHCO_3$ (75 mL), and brine (75 mL), dried over $MgSO_4$, and evaporated to dryness. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH 95:5) to give **5** (1.73 g, 5.78 mmol, 99%) as a white solid of mp 70−71 °C; R_f = 0.49 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{23}$ +20.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (CD_3OD, 500 MHz): δ 5.86 (ddd, *J* = 5.5, 10.5, 17.2 Hz, 1H), 5.30 (td, *J* = 1.6, 17.2 Hz, 1H), 5.14 (td, *J* = 1.6, 10.5 Hz, 1H), 4.34 (tdd, *J* = 1.4, 3.4, 5.5 Hz, 1H), 3.98−3.92 (m, 1H), 3.68 (dd, *J* = 6.4, 10.9 Hz, 1H), 3.55 (dd, *J* = 6.4, 10.9 Hz, 1H), 2.21 (dt, *J* = 1.5, 7.5 Hz, 2H), 1.65−1.55 (m, 2H), 1.35−1.25 (m, 16H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (CD_3OD, 126 MHz): δ 176.7, 139.9, 116.0, 72.0, 62.4, 56.4, 37.3, 33.2, 30.9, 30.8, 30.7, 30.5, 27.3, 23.9, 14.6; IR ν_{max} 3364, 2923, 2853, 2415, 1622, 1456, 1054, 991, 922 cm^{-1}; HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{17}H_{34}O_3N^+$, 300.2533; found 300.2523.

*N-((4R,5R)-2,2-Dimethyl-4-vinyl-1,3-dioxan-5-yl)dodecanamide (**8**).* A solution of **5** (1.29 g, 4.32 mmol) in acetone (20 mL) was treated with 2,2-dimethoxypropane (5.3 mL, 43.24 mmol) and BF_3·Et_2O (55 μL, 0.43 mmol). The mixture was stirred for 3 h at ambient temperature. NEt_3 (0.5 mL) was added, and volatiles were removed under reduced pressure. The residue was purified by flash chromatography (*n*-hexane/ethyl acetate 2:1) to give **8** (1.37 g, 4.05 mmol, 94%) as colorless oil; R_f = 0.28 (*n*-hexan/ethyl acetate 3:1); $[\alpha]_D^{23}$ +5.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.11 (d, *J* = 9.2 Hz, 1H), 5.71 (ddd, *J* = 4.4, 10.7, 17.3 Hz, 1H), 5.31 (td, *J* = 1.7, 17.3 Hz, 1H), 5.19 (td, *J* = 1.7, 10.7 Hz, 1H), 4.56 (dd, *J* = 1.7, 4.3 Hz, 1H), 4.12 (dd, *J* = 1.8, 12.0 Hz, 1H), 3.97 (dd, *J* = 1.8, 9.2 Hz, 1H), 3.75 (dd, *J* = 1.8, 12.0 Hz, 1H), 2.20 (dt, *J* = 3.1, 7.6 Hz, 2H), 1.65−1.57 (m, 2H), 1.50 (s, 3H), 1.46 (s, 3H), 1.33−1.21 (m, 16H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 172.9, 134.7, 116.6, 99.2, 71.3, 64.6, 45.5, 36.8, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 25.7, 22.7, 18.5, 14.1; IR ν_{max} 3322, 2924, 2854, 1651, 1505, 1380, 1269, 1237, 1199, 1087, 985, 856 cm^{-1}; HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{20}H_{38}O_3N^+$, 340.2846; found 340.2838.

*N-((4S,5R)-4-((R)-1,2-Dihydroxyethyl)-2,2-dimethyl-1,3-dioxan-5-yl)dodecanamide (**4**).* Alkene **8** (1.32 g, 3.9 mmol) was dissolved in THF (20 mL), and K_2OsO_4·$2H_2O$ (75 mg, 0.19 mmol) and NMO (50% in H_2O, 2.5 mL, 11.7 mmol) were added. The mixture was stirred for 18 h at room temperature. Water (50 mL) was added, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (150 mL), dried over $MgSO_4$, and evaporated to dryness. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate 1:4) to give diol **4** (1.12 g, 3.0 mmol, 77%) as a colorless oil; R_f = 0.30 (*n*-hexane/ethyl acetate 1:2); $[\alpha]_D^{23}$ +40.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.35 (d, *J* = 7.9 Hz, 1H), 5.04 (d, *J* = 3.7 Hz, 1H), 4.21 (dd, *J* = 2.1, 12.2 Hz, 1H), 3.97 (dd, *J* = 1.5, 8.5 Hz, 1H), 3.88 (dd, *J* = 1.2, 9.2 Hz, 1H), 3.80−3.73 (m, 2H), 3.57 (td, *J* = 5.6, 11.3 Hz, 1H), 3.34−3.27 (m, 1H), 2.30 (dt, *J* = 1.4, 7.7 Hz, 2H); 2.24−2.16 (m, 1H), 1.70−1.62 (m, 2H), 1.47 (s, 3H), 1.40 (s, 3H), 1.37−1.22 (m, 16H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 175.3, 99.3, 71.7, 69.4, 64.3, 63.1, 44.0, 36.5, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 25.7, 22.7, 18.5, 14.1; IR ν_{max} 3316, 2923, 2853, 1640, 1528, 1460, 1382, 1271, 1199, 1087, 849, 662 cm^{-1}; HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{20}H_{40}O_5N^+$, 374.2901; found, 374.2894. The *anti*/*syn* ratio of 5:1 was determined by analysis of ^{1}H NMR spectrum of the crude product.

Mosher Esters of Diol 4. *N-((4S,5R)-4-((R)-2′-((tert-Butyldimethylsilyl)oxy)-1′-hydroxyethyl)-2,2-dimethyl-1,3-dioxan-5-yl)dodecanamide.* A solution of diol **4** (100 mg, 0.27 mmol) in CH_2Cl_2 (20 mL) was treated with imidazole (36 mg, 0.54 mmol) and TBSCl (44 mg, 0.29 mmol) and was stirred at ambient temperature for 18 h. Saturated aqueous NH_4Cl (10 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by flash chromatography (*n*-

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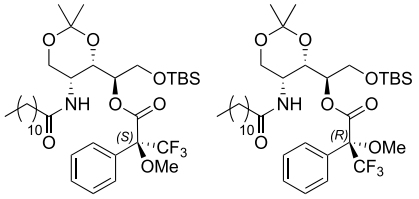
J. Org. Chem. 2021, 86, 1868−1873

hexane/ethyl acetate 5:1) to give the primary TBS-ether of diol **4** as colorless oil (121 mg, 0.25 mmol, 93%); R_f = 0.50 (*n*-hexane/ethyl acetate 2:1); $[\alpha]_D^{23}$ +50.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.28 (d, *J* = 8.9 Hz, 1H), 4.40 (s, 1H), 4.18 (dd, *J* = 1.8, 12.2 Hz, 1H), 4.04 (dd, *J* = 1.5, 8.9 Hz, 1H), 3.99 (dd, *J* = 1.5, 9.2 Hz, 1H), 3.78 (dd, *J* = 2.1, 10.7 Hz, 1H), 3.76 (dd, *J* = 1.8, 12.2 Hz, 1H), 3.68 (dd, *J* = 4.3, 10.7 Hz, 1H), 3.26 (ddd, *J* = 2.1, 4.3, 9.2 Hz, 1H), 2.27 (t, *J* = 7.6 Hz, 2H), 1.65 (quin, *J* = 7.6 Hz, 2H), 1.46 (s, 3H), 1.39 (s, 3H), 1.36−1.18 (m, 16H), 0.90 (s, 9H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 174.6, 99.2, 70.3, 70.2, 64.7, 63.2, 43.8, 36.6, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 26.0, 25.8, 22.7, 18.6, 18.5, 14.1, −5.4, −5.3; IR ν_{max} 3318, 2957, 2925, 2855, 1642, 1524, 1462, 1391, 1252, 1199, 1121, 1090, 834, 777 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{54}O_5NSi^+$, 488.3766; found, 488.3767.

(R)-2′-((tert-Butyldimethylsilyl)oxy)-1′-((4S,5R)-5-dodecanamido-2,2-dimethyl-1,3-dioxan-4-yl) ethyl (S)-/(R)-3″,3″,3″-trifluoro-2″-methoxy-2″-phenylpropanoate (S- and R-Mosher esters).



***S*-Mosher ester** ***R*-Mosher ester**

A solution of the primary TBS-ether of diol **4** (35 mg, 72 μmol) in dry CH_2Cl_2 (1 mL) was treated with 4-dimethylaminopyridine (DMAP) (18 mg, 140 μmol) and (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl; 16 μL, 86 μmol). The mixture was stirred at ambient temperature for 18 h, and volatiles were removed *in vacuo*. The crude products were purified by flash chromatography (*n*-hexane/ethyl acetate 5:1) to give *S*-Mosher ester (40 mg, 79%) or *R*-Mosher ester (24 mg, 48%) as colorless oils; R_f = 0.34 (*n*-hexane/ethyl acetate 5:1); IR ν_{max} 3440, 2927, 2656, 1755, 1678, 1500, 1463, 1383, 1254, 1169, 1108, 1017, 977, 833, 776, 719 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{36}H_{61}O_7NF_3Si^+$, 704.4163; found, 704.4161; *S*-Mosher ester: $[\alpha]_D^{23}$ −35.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61−7.56 (m, 2H), 7.42−7.37 (m, 3H), 6.00 (d, *J* = 9.2 Hz, 1H), 5.20 (td, *J* = 3.8, 7.9 Hz, 1H), 4.32 (dd, *J* = 1.8, 7.9 Hz, 1H), 3.97 (dd, *J* = 1.8, 12.1 Hz, 1H), 3.88 (qd, *J* = 1.8, 9.2 Hz, 1H), 3.82 (t, *J* = 3.8 Hz, 2H), 3.73 (dd, *J* = 1.8, 12.1 Hz, 1H), 3.62−3.58 (m, 3H), 2.07 (dt, *J* = 1.7, 7.5 Hz, 2H), 1.57 (quin, *J* = 7.5 Hz, 2H), 1.46 (s, 3H), 1.40 (s, 3H), 1.32−1.21 (m, 16 H), 0.89 (s, 9H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 172.6, 165.5, 132.7, 129.54, 128.4, 127.4, 123.3 ($^1J_{FC}$ = 288.8 Hz), 99.6, 84.5 ($^2J_{FC}$ = 28.2 Hz), 74.1, 67.8, 64.8, 60.1, 55.6, 42.9, 36.6, 31.9, 29.6, 29.5, 29.4, 29.3, 25.7, 25.6, 22.7, 18.5, 18.1, 14.1, −5.6, −5.7; *R*-Mosher ester: $[\alpha]_D^{23}$ −15.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.59−7.53 (m, 2H), 7.43−7.37 (m, 3H), 6.13 (d, *J* = 8.9 Hz, 1H), 5.14 (td, *J* = 3.8, 7.8 Hz, 1H), 4.39 (dd, *J* = 1.8, 7.8 Hz, 1H), 4.01 (dd, *J* = 1.8, 12.0 Hz, 1H), 3.95 (qd, *J* = 1.8, 8.9 Hz, 1 H), 3.80 (dd, *J* = 1.8, 12.0 Hz, 1 H), 3.73 (ddd, *J* = 3.8, 11.0, 17.1 Hz, 2 H), 3.56−3.53 (m, 3 H), 2.08 (t, *J* = 7.9 Hz, 2 H), 1.61−1.54 (m, 2 H), 1.47 (s, 3 H), 1.43 (s, 3 H), 1.32−1.22 (m, 17 H), 0.87 (t, *J* = 7.0 Hz, 4 H), 0.83 (s, 9 H), −0.01 (s, 3 H), −0.03 (s, 3 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 172.9, 165.9, 132.0,129.6, 128.5, 127.7, 123.2 ($^1J_{FC}$ = 288.8 Hz), 99.6, 84.9 ($^2J_{FC}$ = 28.2 Hz), 74.3, 67.5, 64.7, 59.7, 55.5, 43.1, 36.6, 31.9, 29.6, 29.5, 29.4, 29.3, 25.7, 25.6, 22.7, 18.5, 18.1, 14.1, −5.6, −5.7. For an analysis[6] confirming the absolute configuration of diol **4** *cf.* the Supporting Information.

*(R)-2-((4S,5R)-5-Dodecanamido-2,2-dimethyl-1,3-dioxan-4-yl)-2-hydroxyethyl palmitate (**9a**).* A solution of **4** (780 mg, 2.01 mmol) in dry CH_2Cl_2 (20 mL) was treated with DMAP (26 mg, 0.20 mmol), EDC·HCl (400 mg, 2.01 mmol), and palmitic acid (477 mg, 2.01 mmol) and stirred for 18 h at ambient temperature. The organic phase was washed with 1M HCl (20 mL), aqueous $NaHCO_3$ (20 mL), and brine (20 mL), dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate 2:1) to give **9a** (806 mg, 1.32 mmol, 82%) as a white solid; mp 52−53 °C; R_f = 0.49 (*n*-hexane/ethyl acetate 2:1); $[\alpha]_D^{23}$ +38.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.34 (d, *J* = 8.5 Hz, 1H), 4.99 (s, 1H), 4.25 (dd, *J* = 2.3, 11.5 Hz, 1H), 4.20 (dd, *J* = 1.7, 12.3 Hz, 1H), 4.12 (dd, *J* = 5.7, 11.5 Hz, 1H), 4.01 (dd, *J* = 1.7, 8.5 Hz, 1H), 3.88 (dd, *J* = 1.2, 9.2 Hz, 1H), 3.77 (dd, *J* = 1.7, 12.3 Hz, 1H), 3.45 (ddd, *J* = 2.3, 5.7, 9.2 Hz, 1H), 2.33 (t, *J* = 7.6 Hz, 2H), 2.30 (dt, *J* = 3.1, 7.3 Hz, 2H), 1.69−1.56 (m, 4H), 1.43 (s, 3H), 1.38 (s, 3H), 1.35−1.19 (m, 40H), 0.87 (t, *J* = 7.3 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 175.3, 173.9, 99.4, 71.1, 67.8, 64.4, 64.3, 43.8, 36.4, 34.2, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 25.7, 24.9, 22.6, 18.4, 14.1; IR ν_{max} 3322, 2922, 2853, 1736, 1644, 1526, 1457, 1381, 1269, 1234, 1199, 1175, 1090, 850 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{36}H_{70}O_6N^+$, 612.5197; found, 612.5189.

*(R)-2-((4S,5R)-5-Dodecanamido-2,2-dimethyl-1,3-dioxan-4-yl)-2-hydroxyethyl tetradecanoate (**9b**).* Analogous to **9a**, ester **9b** (647 mg, 1.11 mmol, 69%) was prepared as a white solid from alcohol **4** (600 mg, 1.61 mmol), DMAP (20 mg, 0.16 mmol), EDC·HCl (308 mg, 1.61 mmol), and myristic acid (367 mg, 1.61 mmol); mp 40−41 °C; R_f = 0.37 (*n*-hexane/ethyl acetate 2:1); $[\alpha]_D^{23}$ +38.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.34 (d, *J* = 8.5 Hz, 1H), 4.97 (s, 1H), 4.23 (dd, *J* = 2.1, 11.5 Hz, 1H), 4.18 (dd, *J* = 1.5, 12.3 Hz, 1H), 4.11 (dd, *J* = 5.6, 11.5 Hz, 1H), 3.99 (dd, *J* = 1.5, 8.5 Hz, 1H), 3.86 (dd, *J* = 1.2, 9.2 Hz, 1H), 3.76 (dd, *J* = 1.5, 12.3 Hz, 1H), 3.43 (ddd, *J* = 2.1, 5.6, 9.2 Hz, 1H), 2.34−2.26 (m, 4H), 1.68−1.56 (m, 4H), 1.41 (s, 3H), 1.37 (s, 3H), 1.34−1.17 (m, 36H), 0.85 (t, *J* = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 175.2, 173.9, 99.3, 71.0, 67.7, 43.8, 36.4, 34.1, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 25.6, 24.9, 22.6, 18.3, 14.0; IR (cm^{-1}, neat) ν_{max} 3344, 2922, 2853, 1737, 1645, 1526, 1461, 1381, 1200, 1090, 850 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{34}H_{66}O_6N^+$, 584.4884; found, 584.4879.

*Nona-2,5-diyn-1-ol (**11**).* CuI (4.60 g, 24.1 mmol), NaI (3.62 g, 24.1 mmol), Cs_2CO_3 (7.86 g, 24.1 mmol), and propargylic alcohol (1.39 mL, 24.1 mmol) were added to a solution of **10** (3.0 g, 18.6 mmol) in dry DMF (25 mL). The mixture was stirred for 18 h at ambient temperature. Saturated aqueous NH_4Cl (50 mL) was added, and the mixture was filtered over celite. The filtrate was extracted with Et_2O (3 × 50 mL), and the combined organic phases were washed with brine (2 × 100 mL), dried over $MgSO_4$, and evaporated to dryness. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate 5:1) to give **11** (2.25 g, 16.5 mmol, 89%) as colorless oil; R_f = 0.12 (*n*-hexane/ethyl acetate 5:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.29−4.23 (m, 2H), 3.22−3.16 (m, 2H), 2.16−2.10 (m, 2H), 1.63 (s, 1H), 1.51 (sxt, *J* = 7.3 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 81.0, 80.9, 79.3, 73.4, 51.3, 22.1, 20.6, 13.5, 9.8; IR ν_{max} 3348, 2964, 2934, 2874, 1729, 1414, 1313, 1113, 1010 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_9H_{13}O^+$, 137.0961; found, 137.0960.

*1-Bromonona-2,5-diyne (**12**).* PBr_3 (0.63 mL, 6.6 mmol) and 0.1 mL pyridine were added to a solution of **11** (2.25 g, 16.5 mmol) in Et_2O (100 mL) at 0 °C. The mixture was stirred for 3 h at 0 °C and brine (100 mL) was added. The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by flash chromatography (*n*-pentane/Et_2O 20:1) to give **12** (3.22 g, 16.2 mmol, 98%) as colorless oil; R_f = 0.50 (*n*-pentane/Et_2O 20:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.91 (t, *J* = 2.3 Hz, 2H), 3.21 (quin, *J* = 2.3 Hz, 2H), 2.13 (tt, *J* = 2.3, 7.2 Hz, 2H), 1.51 (sxt, *J* = 7.2 Hz, 2H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 82.1, 81.2, 75.2, 72.9, 22.1, 20.6, 14.9,

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J. Org. Chem. 2021, 86, 1868−1873

13.5, 10.1; IR ν_{max} 2962, 2934, 2872, 1718, 1463, 1411, 1313, 1209, 1123 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_9H_{12}Br^+$, 199.0117; found, 199.0117.

*Methyl hexadeca-6,9,12-triynoate (**13**).* Analogous to **11**, ester **13** (937 mg, 3.63 mmol, 76%) was prepared as colorless oil from **12** (950 mg, 4.77 mmol), 6-heptynoic acid methyl ester (870 mg, 6.20 mmol), CuI (1.18 g, 6.20 mmol), NaI (930 mg, 6.20 mmol), and Cs_2CO_3 (2.02 g, 6.20 mmol); R_f = 0.27 (*n*-hexane/ethyl acetate 30:1); ^1H NMR ($CDCl_3$, 500 MHz): δ 3.69 (s, 3H), 3.16−3.14 (m, 4H), 2.34 (t, *J* = 7.5 Hz, 2H), 2.20 (tt, *J* = 2.2, 7.1 Hz, 2H), 2.15 (tt, *J* = 2.2, 7.1 Hz, 2H), 1.77−1.69 (m, 2H), 1.58−1.50 (m, 4H), 0.98 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 173.9, 80.7, 80.1, 74.9, 74.7, 74.2, 73.8, 51.5, 33.6, 28.1, 24.1, 22.1, 20.7, 18.4, 13.5, 9.8; IR ν_{max} 2936, 1735, 1435, 1317, 1198, 1172, 1147 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{17}H_{23}O_2^+$ 259.1693, found 259.1693.

*Methyl (6Z,9Z,12Z)-hexadeca-6,9,12-trienoate (**14**).* A suspension of $Ni(OAc)_2{\cdot}4H_2O$ (566 mg, 2.28 mmol) in EtOH (10 mL) was treated with $NaBH_4$ (86 mg, 2.28 mmol) at 0 °C. The mixture was stirred under a hydrogen atmosphere at ambient temperature for 30 min. Ethylene diamine (610 μL, 9.13 mmol) and **13** (590 mg, 2.28 mmol) were added, and stirring under a hydrogen atmosphere at ambient temperature was continued for 3 h. The resulting suspension was filtered over celite, and saturated aqueous NH_4Cl (50 mL) was added. The aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate 30:1) to give **14** (561 mg, 2.12 mmol, 98%) as colorless oil; R_f = 0.27 (*n*-hexane/ethyl acetate 30:1); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.44−5.31 (m, 6H), 2.80 (t, *J* = 5.8 Hz, 2H), 2.31 (t, *J* = 7.6 Hz, 2H), 2.11−2.01 (m, 4H), 1.69−1.60 (m, 2H), 1.44−1.33 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 174.2, 130.2, 129.6, 128.4, 128.2, 128.1, 127.8, 51.5, 34.0, 29.3, 29.1, 26.9, 25.7, 25.6, 24.6, 22.8, 13.8; IR ν_{max} 3011, 2929, 2858, 1741, 1436, 1198, 1171, 713 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{29}O_2^+$, 265.2162; found, 265.2162.

*(6Z,9Z,12Z)-Hexadeca-6,9,12-trienoic acid (**15**).* Ester **14** (550 mg, 2.08 mmol) in THF/H_2O 1:1 (10 mL) was treated with $LiOH{\cdot}H_2O$ (175 mg, 4.16 mmol), and the mixture was stirred for 18 h at ambient temperature. 1 M HCl was added (20 mL), and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate 3:1) to give **15** (458 mg, 1.83 mmol, 88%) as colorless oil; R_f = 0.4 (*n*-hexane/ethyl acetate 3:1); ^1H NMR ($CDCl_3$, 500 MHz): δ 11.51 (s, 1 H), 5.50−5.28 (m, 6H), 2.81 (t, *J* = 6.0 Hz, 4H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.13−2.00 (m, 4H), 1.71−1.61 (m, 2H), 1.47−1.33 (m, 4H), 0.91 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 179.9, 130.2, 129.5, 128.4, 128.3, 128.0, 127.8, 33.9, 29.3, 29.0, 26.8, 25.6, 24.3, 22.8, 13.8; IR ν_{max} 3011, 2928, 2859, 1707, 1413, 1287, 1233, 928, 711 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{27}O_2^+$, 251.2006; found, 251.2009.

*Methyl undeca-4,7-diynoate (**16**).* Analogous to **13**, ester **16** (1.21 mg, 6.30 mmol, 68%) was prepared as colorless oil from **10** (1.50 g, 9.3 mmol), 4-pentynoic acid methyl ester (1,35 g, 12.0 mmol), CuI (2.29 g, 12.0 mmol), NaI (1.80 g, 12.0 mmol), and Cs_2CO_3 (3.92 g, 12.0 mmol); R_f = 0.3 (*n*-hexane/ethyl acetate 30:1); ^1H NMR ($CDCl_3$, 500 MHz): δ 3.67 (s, 3H), 3.09 (quin, *J* = 2.3 Hz, 2H), 2.53−2.43 (m, 4H), 2.11 (tt, *J* = 2.3, 7.1 Hz, 2H), 1.49 (sxt, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 172.4, 80.5, 78.2, 75.4, 74.2, 51.7, 33.3, 22.1, 20.6, 14.6, 13.4, 9.6; IR ν_{max} 2962, 2935, 2875, 1737, 1437, 1366, 1314, 1198, 1166, 1038 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{17}O_2^+$, 193.1223; found, 193.1225.

*Methyl (4Z,7Z)-undeca-4,7-dienoate (**17**).* Analogous to **14**, ester **17** (1.46 g, 7.42 mmol, 95%) was prepared as colorless oil from **16** (1.50 g, 7.81 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (1.94 g, 7.81 mmol), $NaBH_4$ (295 mg, 7.81 mmol), and ethylene diamine (2.1 mL, 31.22 mmol); R_f = 0.3 (*n*-hexane/ethyl acetate 30:1); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.44−5.29 (m, 4H), 3.66 (s, 3H), 2.79 (t, *J* = 7.0 Hz, 2H), 2.42−2.34 (m, 4H), 2.03 (q, *J* = 7.3 Hz, 2H), 1.37 (sxt, *J* = 7.3 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 173.6, 130.2, 129.7, 127.6, 127.5, 51.5, 34.0, 29.3, 25.5, 22.8, 13.8; IR ν_{max} 3011, 2957, 2872, 1740, 1436, 1360, 1196, 1160, 717 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{21}O_2^+$ 197.1536, found 197.1538.

*(4Z,7Z)-Undeca-4,7-dienoic acid (**18**).* Analogous to **15**, carboxylic acid **18** (700 mg, 3.84 mmol, 98%) was prepared as colorless oil from **17** (770 mg, 3.92 mmol) and $LiOH{\cdot}H_2O$ (330 mg, 7.85 mmol); R_f = 0.35 (*n*-hexane/ethyl acetate 3:1); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.46−5.30 (m, 4H), 2.80 (t, *J* = 7.0 Hz, 2H), 2.43−2.36 (m, 4H), 2.03 (q, *J* = 7.3 Hz, 2H), 1.38 (sxt, *J* = 7.3 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 179.1, 130.3, 129.9, 127.5, 127.2, 34.0, 29.3, 25.6, 22.7, 22.5, 13.8; IR ν_{max} 3011, 2958, 2929, 2873, 1708, 1412, 1279, 1250, 1211, 931, 712 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{19}O_2^+$, 183.1379; found, 183.1380.

*(R)-1-((4S,5R)-5-Dodecanamido-2,2-dimethyl-1,3-dioxan-4-yl)-2-(palmitoyloxy)ethyl (6Z,9Z,12Z)-hexadeca-6,9,12-trienoate (**19a**).* A solution of **9a** (244 mg, 0.40 mmol) in dry CH_2Cl_2 (10 mL) was treated with DMAP (98 mg, 0.80 mmol), EDC·HCl (92 mg, 0.48 mmol), and **15** (100 mg, 0.4 mmol) and stirred for 18 h at ambient temperature. The organic phase was washed with 1M HCl (20 mL), aqueous $NaHCO_3$ (20 mL), and brine (20 mL), dried over $MgSO_4$, and evaporated to dryness. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate 5:1) to give **19a** (250 mg, 0.30 mmol, 74%) as colorless oil; R_f = 0.4 (*n*-hexane/ethyl acetate 5:1); $[\alpha]_D^{23}$ +9.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.07 (d, *J* = 10.1 Hz, 1H), 5.43−5.30 (m, 6H), 4.93 (ddd, *J* = 2.4, 4.6, 9.7 Hz, 1H), 4.38 (dd, *J* = 2.0, 12.2 Hz, 1H), 4.19 (dd, *J* = 2.0, 9.7 Hz, 1H), 4.14−4.06 (m, 3H), 3.71 (dd, *J* = 1.5, 12.2 Hz, 1H), 2.84−2.76 (m, 4H), 2.39−2.23 (m, 4H), 2.22−2.13 (m, 2H), 2.10−1.97 (m, 4H), 1.65−1.54 (m, 6H), 1.46 (s, 3H), 1.41 (s, 3H), 1.41−1.35 (m, 4H), 1.29−1.21 (m, 40H) 0.91 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 173.4, 172.6, 172.3, 130.1, 129.7, 128.4, 128.1, 128.0, 127.8, 99.5, 68.8, 68.3, 65.1, 62.1, 41.9, 36.7, 34.1, 33.9, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 26.9, 25.6, 25.5, 24.9, 24.2, 22.8, 22.7, 18.3, 14.1, 13.8; IR ν_{max} 2922, 2853, 1744, 1679, 1501, 1462, 1381, 1236, 1199, 1142, 1093, 843, 721 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{52}H_{94}O_7N^+$, 844.7025; found, 844.7018.

*(R)-2-((4S,5R)-5-Dodecanamido-2,2-dimethyl-1,3-dioxan-4-yl)-2-(((4Z,7Z)-undeca-4,7-dienoyl)oxy)ethyl tetradecanoate (**19b**).* Analogous to **19a**, ester **19b** (658 mg, 0.88 mmol, 88%) was prepared as colorless oil from alcohol **9b** (584 mg, 1.00 mmol), DMAP (245 mg, 2.00 mmol), EDC·HCl (230 mg, 1.20 mmol), and acid **18** (182 mg, 1.00 mmol); R_f = 0.37 (*n*-hexane/ethyl acetate 2:1); $[\alpha]_D^{23}$ +10.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.09 (d, *J* = 9.8 Hz, 1H), 5.45−5.29 (m, 4H), 4.94 (ddd, *J* = 2.1, 4.3, 9.8 Hz, 1H), 4.37 (dd, *J* = 2.1, 12.2 Hz, 1H), 4.20 (dd, *J* = 2.0, 9.8 Hz, 1H), 4.14−4.07 (m, 3H), 3.71 (dd, *J* = 1.8, 12.2 Hz, 1H), 2.80 (t, *J* = 6.0 Hz, 2H), 2.45−2.32 (m, 4H), 2.30 (dt, *J* = 1.5, 7.5 Hz, 2H), 2.23−2.11 (m, 2H), 2.06−2.00 (m, 2H), 1.64−1.55 (m, 4H), 1.46 (s, 3H), 1.41 (s, 3H), 1.40−1.34 (m, 2H), 1.32−1.22 (m, 36H) 0.90 (t, *J* = 7.3 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 173.4, 172.6, 171.9, 130.2, 129.4, 127.8, 99.5, 68.8, 68.4, 65.1, 62.1, 41.9, 36.7, 34.11, 33.9, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 25.6, 25.5, 24.9, 22.8, 22.7, 22.4, 18.3, 14.1, 13.8; IR ν_{max} 2923, 2853, 1744, 1677, 1505, 1464, 1380, 1236, 1199, 1147, 1086, 843, 721 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{45}H_{82}O_7N^+$, 748.6086; found, 748.6088.

*Bathymodiolamide A (**1**).* A solution of **19a** (250 mg, 0.30 mmol) in 5 mL MeOH was treated with pTsOH (25 mg, 0.15 mmol) and stirred for 2.5 h at ambient temperature. Volatiles were removed under reduced pressure, and the crude product was purified by flash chromatography (*n*-hexane/ethyl acetate 1:1) to give **1** (223 mg, 0.28 mmol, 94%) as a white solid; mp 46−47 °C; R_f = 0.39 (*n*-hexane/ethyl acetate 1:1); $[\alpha]_D^{23}$ +14.8 (*c* 0.08, MeOH) {lit[1]: $[\alpha]_D^{23}$ +10.8 (*c* 0.08, MeOH)}; ^1H NMR (CD_3OD, 500 MHz): δ 5.43−5.31 (m, 6H), 4.92−4.89 (m, 1H), 4.62 (dd, *J* = 2.3, 12.1 Hz, 1H), 4.12 (dd, *J* = 5.8, 12.1 Hz, 1H), 4.12−4.09 (m, 1H), 4.04 (dd, *J* = 1.5, 9.5 Hz, 1H), 3.61 (dd, *J* = 8.2, 10.7 Hz, 1H), 3.53 (dd, *J* = 5.8, 10.7 Hz, 1H),

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J. Org. Chem. 2021, 86, 1868−1873

2.84−2.82 (m, 4H), 2.38−2.27 (m, 4H), 2.22−2.15 (m, 2H), 2.14−2.02 (m, 4H), 1.66−1.55 (m, 6H), 1.45−1.36 (m, 4H), 1.36−1.24 (m, 40H), 0.93 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.3 Hz, 6H); $^{13}C\{^1H\}$ NMR (CD_3OD, 126 MHz): δ 176.5, 175.3, 174.1, 131.1, 130.9, 129.5, 129.4, 129.3, 129.2, 71.8, 68.2, 64.3, 62.5, 51.9, 37.3, 35.2, 33.3, 31.0, 30.8, 30.7, 30.6, 30.5, 30.4, 28.2, 27.2, 26.8, 26.2, 25.4, 24.0, 23.9, 14.7, 14.4; IR ν_{max} 3320, 2922, 2853, 1744, 1633, 1457, 1377, 1173, 1057, 720 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{49}H_{90}O_7N^+$, 804.6712; found, 804.6703.

(2R,3S,4R)-Bathymodiolamide B (2). Analogous to **1**, bathymodiolamide B (184 mg, 0.26 mmol, 97%) was prepared as a white solid from acetonide **19b** (200 mg, 0.27 mmol) and pTsOH (23 mg, 0.14 mmol); mp 43−44 °C; R_f = 0.3 (n-hexane/ethyl acetate 1:1); $[\alpha]_D^{23}$ +6.7 (c 0.08, MeOH) {lit[1]: $[\alpha]_D^{23}$ +10.8 (c 0.08, MeOH}; ^1H NMR (CD_3OD, 500 MHz): δ 5.41−5.32 (m, 4H), 4.93−4.89 (m, 1H), 4.60 (dd, J = 2.4, 12.2 Hz, 1H), 4.14 (dd, J = 5.8, 12.2 Hz, 1H), 4.12−4.09 (m, 1H), 4.05 (dd, J = 1.5, 9.5 Hz, 1H), 3.61 (dd, J = 8.5, 10.7 Hz, 1H), 3.53 (dd, J = 5.8, 10.7 Hz, 1H), 2.84−24.2 (m, 2H), 2.42−2.32 (m, 4H), 2.30 (t, J = 7.3 Hz, 2H), 2.24−2.12 (m, 2H), 2.07 (q, J = 6.7 Hz, 2H), 1.61−1.57 (m, 4H), 1.44−1.36 (m, 2H), 1.36−1.24 (m, 36H), 0.93 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.3 Hz, 9H); $^{13}C\{^1H\}$ NMR (CD_3OD, 126 MHz): δ 176.5, 175.3, 173.6, 131.1, 130.5, 129.2, 71.9, 68.2, 62.5, 51.9, 37.3, 35.3, 35.2, 33.3, 31.0, 30.8, 30.7, 30.6, 30.5, 30.4, 27.2, 26.7, 26.2, 24.1, 23.9, 23.8, 14.7, 14.4; IR ν_{max} 3363, 2920, 2853, 1745, 1640, 1457, 1377, 1152, 1061, 722 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{42}H_{78}O_7N^+$, 708.5772; found, 708.5765.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02726.

Comparison of synthetic and isolated bathymodiolamides A and B; analysis of the Mosher esters of alcohol **4**; NMR spectra of all compounds; and cell culture conditions and inhibition of cell growth (PDF)

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Notes

The authors declare no competing financial interest.

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